Complete Summary

GUIDELINE TITLE

American Association of Clinical Endocrinologists and Associazione Medici Endocrinologi medical guidelines for clinical practice for the diagnosis and management of thyroid nodules.

BIBLIOGRAPHIC SOURCE(S)

AACE/AME Task Force on Thyroid Nodules. American Association of Clinical Endocrinologists and Associazione Medici Endocrinologi medical guidelines for clinical practice for the diagnosis and management of thyroid nodules. Endocr Pract 2006 Jan-Feb;12(1):63-102. [142 references]

GUIDELINE STATUS

This is the current release of the guideline.

This guideline updates a previous version: AACE clinical practice guidelines for the diagnosis and management of thyroid nodules. Jacksonville (FL): AACE; 1996. 16 p. (AACE clinical guidelines; no. 1996).

COMPLETE SUMMARY CONTENT

SCOPE

DISEASE/CONDITION(S)

Thyroid nodules

GUIDELINE CATEGORY

Diagnosis
Management
Treatment

CLINICAL SPECIALTY

Endocrinology
Family Practice
Internal Medicine
Pediatrics

INTENDED USERS

Physicians

GUIDELINE OBJECTIVE(S)

To provide recommendations for the diagnosis and management of thyroid nodules

TARGET POPULATION

Patients with a nodular thyroid

INTERVENTIONS AND PRACTICES CONSIDERED

Diagnosis

1. History and physical examination
2. Ultrasonography of thyroid gland
3. Fine-needle aspiration (FNA) biopsy of thyroid nodules
4. Radionuclide scanning
5. Laboratory evaluation, including serum thyroid-stimulating hormone
6. Magnetic resonance (MR) and computed tomography (CT) imaging of the thyroid (considered, but not indicated in routine nodal evaluation)
7. Histochemical markers (considered, but not recommended)

Management/Treatment

1. Thyroidectomy
2. Levothyroxine suppression treatment
3. Thyroid lobectomy and isthmectomy
4. Percutaneous ethanol injection
5. Radioiodine treatment
6. Laser thermal ablation

MAJOR OUTCOMES CONSIDERED

- Accuracy of diagnostic tests
- Patient morbidity
- Cost-effectiveness of care

- Adverse effects

METHODOLOGY

METHODS USED TO COLLECT/SELECT EVIDENCE

Hand-searches of Published Literature (Primary Sources)
Hand-searches of Published Literature (Secondary Sources)
Searches of Electronic Databases

DESCRIPTION OF METHODS USED TO COLLECT/SELECT THE EVIDENCE

The authors searched for the primary evidence to support the current guidelines by using a "clinical question" method. Each topic covered by the guidelines was translated to a related question. Each clinical question can be answered appropriately only by certain types of clinical studies and not by others. Accordingly, the bibliographic research was conducted by selecting the studies able to yield a methodologically reliable answer to each question.

The first step was to select pertinent published reports. The United States National Library of Medicine Medical Subject Headings (MeSH) database was used as a terminologic filter. Appropriate MeSH terms were identified, and care was exercised to select them on a sensitive rather than a specific basis. The MeSH terms and their proper combination enabled the authors to retrieve the reports pertinent to a specific issue.

The second step was to select relevant published studies. Beginning with the pertinent reports indexed with the appropriate MeSH terminologic filters, the authors applied the PubMed clinical queries methodologic filters. The clinical queries are grouped into 4 categories: diagnosis, etiology, prognosis, and therapy. For each clinical question, a proper complex search string is available. From the combination of terminologic (MeSH terms) and methodologic filters (clinical queries), the relevant studies, designed to provide a reliable answer to the question, were selected.

After the relevant published studies had been retrieved, the bibliographic research continued by looking for further evidence cited in the bibliography of each report and by following the Related Articles link listed next to each item in MEDLINE.

Meta-analyses were searched, both in MEDLINE and in the Cochrane Library. Three methods were used to search for meta-analyses in MEDLINE:

- Selection of "Meta-Analysis" from the "Publication Type" menu on the "Limits" tab of the PubMed main page
- Application of function "Find Systematic Reviews" on the "Clinical Queries" PubMed page
- Use of Hunt and McKibbon's complex string for systematic reviews:

  AND (meta-analysis [pt] OR meta-anal* [tw] OR metaanal* [tw] OR (quantitative* review* [tw] OR quantitative* overview* [tw]) OR (systematic* review* [tw] OR systematic* overview* [tw]) OR

(methodologic* review* [tw] OR methodologic* overview* [tw]) OR (review [pt] AND medline [tw]))

The Cochrane Library was browsed by entering free terms in the search window.

Guidelines were searched in MEDLINE and in several guidelines databases. Two methods were used to search for guidelines in MEDLINE:

- Selection of "Practice Guidelines" from the "Publication Type" menu on the "Limits" tab of the PubMed main page
- Use of the following GIMBE-Gruppo Italiano Medicina Basata sulle Evidenze complex string for the guidelines:

  "guideline" [pt] OR "practice guideline" [pt] OR "health planning guidelines" [mh] OR "consensus development conference" [pt] OR "consensus development conference, nih" [pt] OR "consensus development conferences" [mh] OR "consensus development conferences, nih" [mh] OR "guidelines" [mh] OR "practice guidelines" [mh] OR (consensus [ti] AND statement [ti])

Guidelines were searched in the following databases: National Guideline Clearinghouse (USA); Agency for Healthcare Research and Quality (USA); Canadian Medical Association--Clinical Practice Guidelines; Canadian Task Force on Preventive Health Care; National Institutes of Health--National Heart, Lung, and Blood Institute (USA); National Health Service Research and Development Health Technology Assessment Programme (UK); National Institute of Clinical Excellence (UK); New Zealand Guidelines Group; PRODIGY Guidance--National Health Service (UK); and the Scottish Intercollegiate Guidelines Network.

NUMBER OF SOURCE DOCUMENTS

Not stated

METHODS USED TO ASSESS THE QUALITY AND STRENGTH OF THE EVIDENCE

Weighting According to a Rating Scheme (Scheme Given)

RATING SCHEME FOR THE STRENGTH OF THE EVIDENCE

Level of Evidence

1. Well-controlled, generalizable, randomized trial
   Adequately powered
   Well-controlled multicenter trial
   Large meta-analysis with quality ratings
   All-or-none evidence
2. Randomized controlled trial--limited body of data
   Well-conducted prospective cohort study
   Well-conducted meta-analysis of cohort studies
3. Methodologically flawed randomized clinical trials
   Observational studies

Case series or case reports
Conflicting evidence with weight of evidence supporting the recommendation

4. Expert consensus
   Expert opinion based on experience
   "Theory-driven conclusions"
   "Unproven claims"

METHODS USED TO ANALYZE THE EVIDENCE

Review of Published Meta-Analyses
Systematic Review

DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE

Not stated

METHODS USED TO FORMULATE THE RECOMMENDATIONS

Not stated

RATING SCHEME FOR THE STRENGTH OF THE RECOMMENDATIONS

Recommendation Grade

A. Homogeneous evidence from multiple well-designed randomized controlled trials with sufficient statistical power
   Homogeneous evidence from multiple well-designed cohort controlled trials with sufficient statistical power
   $\geq$1 conclusive level 1 publications demonstrating benefit >> risk
B. Evidence from at least one large well-designed clinical trial, cohort or case-controlled analytic study, or meta-analysis
   No conclusive level 1 publication; $\geq$1 conclusive level 2 publications demonstrating benefit >> risk
C. Evidence based on clinical experience, descriptive studies, or expert consensus opinion
   No conclusive level 1 or 2 publication; $\geq$1 conclusive level 3 publications demonstrating benefit >> risk
   No conclusive risk at all and no conclusive benefit demonstrated by evidence
D. Not rated
   No conclusive level 1, 2, or 3 publication demonstrating benefit >> risk
   Conclusive level 1, 2, or 3 publication demonstrating risk >> benefit

COST ANALYSIS

A formal cost analysis was not performed and published cost analyses were not reviewed.

METHOD OF GUIDELINE VALIDATION

Peer Review

DESCRIPTION OF METHOD OF GUIDELINE VALIDATION

Twenty-five physicians are acknowledged as reviewers in the guideline document.

RECOMMENDATIONS

MAJOR RECOMMENDATIONS

The recommendation grades (A-D) and levels of evidence (1-4) are defined at the end of the "Major Recommendations" field.

Note from the National Guideline Clearinghouse (NGC): The following recommendations are taken from the Appendices to the original guideline document: Appendix 1: Practical Tips, Appendix 2: Summary of Recommendations for Diagnosis of Thyroid Nodules, and Appendix 3: Summary of Recommendations for Management and Treatment of Thyroid Nodules.

Practical Tips

The following are suggestions for care of patients with nodular thyroid disease, based on Task Force consensus and other expert opinions (grade D).

Minimal Requirements for Ultrasonography (US) Equipment

Overall

Advances in electronics and US technology have decreased the cost of US equipment and made it possible to have dedicated instruments for thyroid evaluation. Phased-array transducers have made mechanical transducers obsolete. The type of equipment required depends on its use.

Thyroid US and US-Fine-Needle Aspiration (FNA)

A 7.5- to 10.0-MHz transducer is sufficient to detect and measure thyroid nodules and to perform US-FNA. Such a transducer allows identification of microcalcifications in real time and usually affords adequate resolution to define the borders of nodules. A linear transducer is generally best for US-FNA. Doppler capability is necessary for determining the vascularity of nodules and sometimes aids in defining the borders of nodules. This level of resolution will allow identification of moderately enlarged lymph nodes (>0.5 cm) in the lateral areas of the neck but may not allow adequate evaluation of lymph node characteristics (hilar line, microcalcifications, cystic necrosis).

For lymph node surveillance in the postoperative thyroid cancer patient, for parathyroid identification, and for performance of percutaneous ethanol injection (PEI), a 10- to 14-MHz transducer is recommended. Power Doppler US is imperative to determine the vascularity of lymph nodes and accelerates the examination by quickly identifying small vessels that may resemble lymph nodes. It also will identify the polar artery in some parathyroid adenomas. The higher resolution allows detection of lymph nodes $\leq$0.5 cm and evaluation of the

aforementioned characteristics. A needle guide attachment is necessary for PEI or laser thermal ablation (LTA), to keep the needle under constant observation during the procedure.

Recommendations for US Evaluation and Reporting

The report of US examination of the thyroid is the main method of sharing information with the referring physician, the general practitioner, and the patient. The description of the US characteristics of the thyroid should provide all the information useful for clinical purposes. A definite diagnosis is not possible with US, but a mere descriptive report is inappropriate if it does not include clinically useful details. Hence, an US report should enable the reader to stratify the nodule under examination on a malignancy risk scale.

In light of the facts that US is a considerably operator-dependent imaging technique and that static images are always unsatisfactory, we recommend paying specific attention to several aspects of the US report.

- Aims of the US report:

  Describe the US elements useful for making a correct diagnosis

  Describe to the patient his or her own situation; make it possible for the patient to follow the nodule over time

- Content requirements:

  Position within the thyroid

  Size--at least the maximal diameter, specifying whether it is longitudinal, anteroposterior, or laterolateral with respect to the lobe anatomy

  Echogenicity (anechoic, hypoechoic, isoechoic, or hyperechoic)

  Presence of a fluid component (mixed nodules)

  Characteristics of the borders

  Presence of peripheral halo

  Internal calcifications (microcalcifications or macrocalcifications)

  If possible, vascular pattern

If the nodule is solitary or only a few well-separated nodules are present, each nodule should be described analytically. If multiple nodules are present, a general description of the thyroid size and structure may be advisable, pointing out with detail the nodule (or nodules) bearing the US characteristics associated with malignant potential (see section 2.2 in the original guideline document), rather than describing only the largest (dominant) nodule.

The report should be typewritten and should indicate clearly the name of the operator and the clinic or hospital. It should be stored in an archive or saved on informatic databases; it should be retrievable.

Static pictures do not provide adequate information for a typically dynamic examination, and their usefulness is limited in US. Nevertheless, inclusion of some images in the report is recommended, especially if particularly important details are detected (suspicious nodules).

- Stylistic suggestions for writing the US report:

  Be concise.

  Point out the pathologic aspects; avoid writing too much about normal findings. Describe normality only if a previous pathologic detail is no longer present (such as a cyst that disappeared) or if a normal report is clinically unexpected (for example, a thyroid nodule suspected by palpation but not shown with US).

  Do not use acronyms, or cite only widely known acronyms.

  Use technical or easily understandable terms, avoiding words with uncertain or multiple meanings.

Recommendations for US-FNA Procedure and Slide Preparation

FNA is the most important diagnostic procedure in the initial evaluation of thyroid nodules, and its accuracy influences subsequent clinical management. The use of US-FNA has increased during the past few years because its accuracy in diagnosing thyroid nodules exceeds that of conventional direct FNA. Proper FNA technique and smear preparation are critical to ensure good results (see section 2.3 in the original guideline document).

Discuss the procedure with the patients to reassure them that serious complications are unlikely. US-FNA is not essential if the nodule is palpable, although US-FNA will be necessary if the initial report is unsatisfactory (nondiagnostic). FNA is safe with use of aspirin or anticoagulants.

US-FNA should be performed by physicians with expertise and interest in thyroid disease. Requisites are experience with palpation of thyroid nodules and with US evaluation of the thyroid, good training, and performance of several US-guided aspirations sufficient to attain expertise.

Commercially available US devices equipped with 7.5- to 10.0-MHz transducers provide a clear and continuous visualization of the thyroid gland and the needle tip on the monitor. Small transducers are especially convenient for US-FNA. After the biopsy sites have been determined, the needle should be inserted through a steering device (US-guided FNA) or just above the center of the transducer (US-assisted FNA). This positioning allows the needle to be inserted nearly perpendicular to the neck, and the tip of the needle (clearly visible as a bright spot on the screen) is observed on the monitor until it reaches the biopsy target.

Because of the direct visualization of the needle, accidental damage to the trachea, carotid artery, jugular vein, or recurrent laryngeal nerve can be avoided. US-guided aspirations require a single operator and a shorter training program than conventional direct FNA, but the flexibility of the procedure is limited by the steering device.

Large needles may produce blood contamination of the aspirated sample. A 25- or 27-gauge needle is suitable for most palpable thyroid nodules, and its use is suggested for the first sampling of the lesion. Aspiration should be ceased as soon as sample appears in the hub of the needle, and smears are then prepared (see section 2.3 in the original guideline document).

With US-FNA, the operator is able to choose the biopsy site after a careful US evaluation. The recommended biopsy sites are as follows:

- In large nodules, the peripheral part of the lesion rather than the central area, because of frequent degenerative changes
- In entirely cystic areas, the center of the lesion should be reached in order to drain the fluid content completely. Cystic fluids should be submitted to the laboratory for evaluation. Most colloid fluids are clear yellow; clear-colorless fluid suggests parathyroid origin, and material should be submitted for measurement of parathyroid hormone. Hemorrhagic fluid suggests a high malignant potential
- In mixed or mostly fluid complex lesions, the needle should be addressed to the root of hubs or pedicles growing into the cystic lumen (the inner area of the pedicle facing the lumen usually contains necrotic debris and cells with degenerative changes). After complete drainage of the fluid, both the solid areas and the peripheral borders of the lesion should be sampled

A definite cytologic diagnosis should always be obtained before PEI treatment of cystic or complex lesions is performed.

Recommendations for Cytologic Reporting

The diagnostic accuracy of FNA is increased with communication between the clinician and the cytopathologist. Thyroid smears should be reviewed by a cytopathologist who has a special interest in thyroid disease.

- Diagnostic pitfalls:

  False-negative results are usually due to inadequate sampling.

  False-positive results are usually due to "suspicious" (indeterminate) findings.

  Gray zones in cytologic reports are follicular neoplasms, Hürthle cell neoplasms, and cytologic findings suggestive of but not diagnostic for papillary carcinoma.

The cytologic diagnosis should be clear to help the clinician manage the condition. Thus, standardization of terminology will improve patient care. Cytologic diagnoses should be organized into 4 categories--inadequate material, benign,

suspicious, and malignant tumors (see Table 5 in the original guideline document).

- Inadequate, unsatisfactory, or nondiagnostic: smears with few or no follicular cells. Action: repeat FNA
- Benign or negative: group including colloid nodule, Hashimoto's thyroiditis, cyst, thyroiditis. Action: observation and follow-up. Cytologically benign but clinically suspicious lesions should be excised
- Suspicious or indeterminate: cytologic results that suggest a malignant lesion but do not completely fulfill the criteria for a definitive diagnosis, including follicular neoplasms, Hürthle cell tumors, and atypical papillary tumors. Action: surgical intervention for definitive diagnosis
- Malignant or positive: group consisting of primary (thyroid) or secondary (metastatic) cancers. Action: surgical consultation and thyroidectomy for primary tumors; search for origin of metastatic disease

Recommendations for ^{131}I Treatment of Multinodular Goiter (MNG)

- Until approval by the United States Food and Drug Administration, the use of recombinant human thyroid-stimulating hormone (rhTSH) to augment radioiodine treatment of MNG is considered "off-label." Its use should be considered in elderly patients or in those with comorbid conditions that preclude anesthesia and surgical treatment.
- Should not be used if the presence of a malignant lesion is suspected, and US-FNA should precede treatment.
- Treat patient with a beta-adrenergic blocking agent or calcium channel blocker during ^{131}I treatment.
- After treatment, patient should undergo follow-up for the development of hypothyroidism or hyperthyroidism.

Recommendations for PEI of Cystic Lesions

Equipment and Procedure

A real-time US system with a 7.5- to 10.0-MHz probe, 95% sterile ethanol, a spinal needle, and a disposable plastic syringe are needed. A 22-gauge, 75-mm spinal needle is used because it is a flexible needle, fitted with a mandrel and long enough to cross the steering device and reach deep thyroid nodules. Near-complete fluid removal is performed to facilitate clear visualization of the needle in the cavity. Without removal of the needle, a syringe containing ethanol is then substituted for the aspirating syringe. The ethanol is slowly injected in amounts of 1 to 10 mL, depending on the volume of the aspirated fluid. It may be useful to ask the patient to talk at regular intervals during the PEI procedure to ensure that the recurrent laryngeal nerves are intact. PEI can be performed by 1 operator, inserting the needle through a guiding device connected to the probe, or by 2 operators, one handling the probe and the other the needle.

- PEI is performed on outpatients; the procedure is rapid (not exceeding 10 minutes); no local or general anesthesia is needed.
- There is no evidence that the serum ethanol level increases after PEI; a limited amount of ethanol is injected into the nodule

- This procedure must be performed by experienced operators with adequate training, to avoid damage to the recurrent laryngeal nerve or other neck structures

Avoidance of Adverse Effects

Adverse effects of PEI are generally mild and transient. Their occurrence depends on the experience of the center. Mild local pain is common but is rapidly self-resolving or can be controlled with low doses of nonsteroidal anti-inflammatory drugs for 1 to 2 days.

Transient dysphonia is rare after PEI treatment of cystic lesions. Special care must be taken to avoid seepage of ethanol outside the nodule. Real-time US monitoring during PEI allows verification of the correct position of the needle tip within the nodule and assessment of the distribution of the injected ethanol, which should be recognizable as an expanding hyperechoic area within the cystic cavity. Ethanol seeping outside the cystic nodule is always attributable to incorrect procedure (usually the displacement of the needle tip) and induces chemical damage to the recurrent laryngeal nerve. After confirmation with laryngoscopy of unilateral vocal cord paresis, corticosteroid therapy (betamethasone, 1.5 mg daily) can be administered for a few days. The patients should be reassured that, in most cases, a complete recovery from vocal cord paresis usually occurs within a few weeks.

In a few patients with severe thyrotoxicosis (rare in cystic autonomously functioning thyroid nodules [AFTN]), the procedure may be followed by transient exacerbation of thyrotoxic symptoms. In most cases, only a slight, transient, and asymptomatic increase in serum thyroid hormone levels is observed.

Subcutaneous and intracapsular hematomas are rare and self-resolving complications, provided the patient is not taking anticoagulants (which should be withdrawn at least 48 hours before PEI).

Serial Assessment of PEI-Treated Nodules

- Thyroid cysts: US of the neck should be performed every 6 months for 2 years and yearly thereafter.
- Nontoxic AFTN: US evaluation as for thyroid cysts. Assess serum thyroid-stimulating hormone (TSH) and thyroxine (T_4) every 3 months after PEI.

Summary of Recommendations for Diagnosis of Thyroid Nodules

History and Physical Examination

- The vast majority of nodules are asymptomatic, and absence of symptoms does not rule out a malignant lesion (grade C).
- Always obtain a biopsy specimen from solitary, firm, or hard nodules. The risk of cancer is similar in a solitary nodule and MNG (grade B).
- Record the following information (grade C):

  Family history of thyroid disease

Previous neck disease or treatment

Growth of the neck mass

Hoarseness, dysphonia, dysphagia, or dyspnea

Location, consistency, and size of the nodule

Neck tenderness or pain

Cervical adenopathy

Symptoms of hyperthyroidism or hypothyroidism

- Factors suggesting increased risk of malignant potential (grade C):

  History of head and neck irradiation

  Family history of medullary thyroid carcinoma (MTC) or multiple endocrine neoplasia type 2 (MEN2)

  Age <20 or >70 years

  Male sex

  Growing nodule

  Firm or hard consistency

  Cervical adenopathy

  Fixed nodule

  Persistent hoarseness, dysphonia, dysphagia, or dyspnea

US and Other Diagnostic Imaging

- US evaluation

  Not recommended (grade C): as a screening test in the general population; in patients with normal thyroid on palpation and low risk for thyroid cancer

  Recommended (grade C): for high-risk patients (history of familial thyroid cancer, multiple endocrine neoplasia type 2, or external irradiation); for all patients with palpable thyroid nodules or MNG; for those with adenopathy suggestive of a malignant lesion

- US reporting criteria (grade C):

Describe position, shape, size, margins, content, echogenic pattern, and, whenever possible, the vascular pattern of the nodule.

Identify the nodule at risk to be malignant, and stratify the nodule with a risk score based on the US findings.

Identify the nodules for FNA biopsy.

- No FNA of nodules <10 mm unless suspicious US findings or high-risk history (grade C)
- US-FNA of nodules of any size in patients with history of neck irradiation or family history of medullary thyroid carcinoma or multiple endocrine neoplasia type 2 (grade C)
- US-FNA should be based on US features (grade B).
- US-FNA should be performed on all hypoechoic nodules ≥10 mm with irregular margins, chaotic intranodular vascular spots, a more-tall-than-wide shape, or microcalcifications (grade B).
- US findings suggestive of extracapsular growth or metastatic cervical lymph nodes warrant an immediate cytologic evaluation, no matter the size of the lesions (grade B).
- In Hashimoto's thyroiditis, the presence of hypoechoic areas due to lymphocytic infiltration should be ruled out before performance of US-FNA on hypoechoic nodules with ill-defined margins (grade C).
- In complex thyroid nodules, obtain US-FNA sampling of the solid component of the lesion before fluid drainage (grade C).
- Thyroid incidentalomas should be followed by US in 6 to 12 months and regularly thereafter (grade D).
- Magnetic resonance imaging (MRI) and computed tomography (CT) are not indicated in routine nodule evaluation (grade C).

FNA Biopsy

- Thyroid FNA biopsy has been established as reliable and safe and has become an integral part of thyroid nodule evaluation.
- Clinical management of thyroid nodules should be guided by the results of ultrasonographic evaluation and FNA biopsy.
- Thyroid smears should be reviewed by a cytopathologist with a special interest in thyroid disease.
- Diagnostic pitfalls:

  False-negative results are usually due to inadequate sampling.

  False-positive results are usually due to "suspicious" findings.

  Gray zones in cytologic reports are follicular neoplasms, Hürthle cell neoplasms, and cytologic findings suggestive of but not diagnostic for papillary carcinoma.

- Standardization of terminology will improve patient care. Cytologic diagnoses should be organized into 4 categories--inadequate material, benign, suspicious, and malignant tumors.

Inadequate, unsatisfactory, or nondiagnostic: smears with few or no follicular cells

Benign or negative: group including colloid nodule, Hashimoto's thyroiditis, cyst, thyroiditis

Suspicious or indeterminate: cytologic results that suggest a malignant lesion but do not completely fulfill the criteria for a definitive diagnosis, including follicular neoplasms, Hürthle cell tumors, and atypical papillary tumors

Malignant or positive: group consisting of primary (thyroid) or secondary (metastatic) cancers

Radionuclide Scanning

- Perform thyroid scintigraphy for a thyroid nodule or MNG if the TSH level is below the lower limit of the normal range or if ectopic thyroid tissue or a retrosternal goiter is suspected (grade B).
- In iodine-deficient areas, perform thyroid scintigraphy for a thyroid nodule or MNG even if the TSH level is in the low-normal range (grade C).
- Use ^{123}I or $^{99m}TcO_4^-$ for thyroid scintigraphy (grade B).

Laboratory Evaluation

- Serum TSH should be tested first, with a third-generation assay (grade B).
- If TSH level is low (<0.5 micro-IU/mL), measure free T_4 and triiodothyronine (T_3); if TSH level is high (>5.0 micro-IU/mL), measure free T_4 and thyroid peroxidase antibody (TPOAb) (grade C).
- Routine assessment of serum thyroglobulin is not recommended for the diagnosis of thyroid nodules or nodular goiter (grade C).
- Serum calcitonin should be measured if FNA or family history suggests medullary thyroid carcinoma (grade B).

Summary of Recommendations for Management and Treatment of Thyroid Nodules

Clinical management of thyroid nodules should be guided by the results of US evaluation and FNA biopsy (grade B).

FNA-Positive Thyroid Nodule

- For a thyroid nodule with positive (malignant) FNA results, surgical treatment is recommended (grade B).
- Review US and cytologic results with the patient and family; discuss treatment options; answer all questions and concerns; recommend surgical excision and discuss potential complications; obtain surgical consultation, preferably with a surgeon experienced in endocrine surgical procedures (grade D).
- For most patients, especially those with differentiated cancers >1 cm, familial disease, and clinical or US evidence of multifocal disease, capsular invasion, or involved nodules, total or near-total thyroidectomy is indicated. Lymph

nodes within the central compartment of the neck (level 6) should be removed, especially if the surgeon has specific training for and experience with thyroid surgical techniques (grade C).

FNA-Negative Thyroid Nodule

- Use of suppressive therapy with levothyroxine (LT_4) may be considered in the following (grade C):

  Patients from geographic areas with iodine deficiency

  Young patients with small thyroid nodules

  Nodular goiters with no evidence of functional autonomy

- Use of LT4 therapy should be avoided in most cases and especially in the following (grade C):

  Large thyroid nodules and goiters, particularly in the presence of symptoms or signs of functional autonomy

  Clinically suspicious lesions or lesions with an inadequate cytologic sample

  Postmenopausal women and men older than 60 years

  Patients with osteoporosis or systemic illnesses

  Patients with cardiovascular disease

- Facts to remember:

  LT4 treatment induces a clinically significant reduction of thyroid nodule volume in only a minority of patients (grade B).

  Long-term TSH suppression may be associated with bone loss and arrhythmia in elderly patients and menopausal women (grade B).

  LT4 treatment should never be fully suppressive (TSH <0.1 micro-IU/mL) (grade C).

  Nodule regrowth is usually observed after cessation of LT_4 therapy (grade C).

  If nodule size decreases, LT_4 therapy should be continued long term (grade D).

  If thyroid nodule grows during LT_4 treatment, reaspiration and possibly surgical treatment should be considered (grade D).

Surgical Treatment

- Surgical indications in a patient with a thyroid nodule include the following:

  Associated local symptoms

  Hyperthyroidism from a large toxic nodule, or hyperthyroidism and concomitant MNG

  Growth of the nodule

  Suspicious or malignant FNA results

- Thyroid lobectomy includes total or near-total lobectomy, with or without isthmectomy. Should the patient require completion thyroidectomy, it is technically easier to perform if the isthmus has previously been resected.
- For a solitary benign nodule, lobectomy plus isthmectomy is sufficient; for bilateral nodules, a near-total thyroidectomy is appropriate.
- The surgical procedure is usually performed with use of general anesthesia; however, some surgeons operate with use of local anesthesia only.
- A thyroid gland that extends substernally can almost always be resected through a cervical approach. Only rarely is median sternotomy necessary to accomplish thyroid lobectomy or total thyroidectomy.
- With experienced surgeons, associated complications are rare.

Percutaneous Ethanol Injection

- PEI should be performed:

  Only by personnel familiar with US-FNA (grade D)

  On cystic thyroid lesions. PEI is highly effective in the treatment of thyroid cysts and complex nodules with a large fluid component (grade B). Because the only alternative to PEI for recurrent and enlarging cysts is surgical resection, PEI is the first-line nonsurgical treatment for recurrent cystic nodules if US-FNA has ruled out a malignant lesion.

- PEI should not be performed:

  On solid, cold nodules, unless surgical treatment is contraindicated (grade D)

  On large or toxic AFTN (nodule volume >5 mL)--the rate of cure is too low and relapse is frequent (grade B)

  On toxic MNGs (grade B)

- PEI may be considered:

  In some small AFTN (nodule volume <5 mL), with a relevant fluid component and not yet completely suppressing the surrounding thyroid parenchyma, if patients are concerned about late hypothyroidism (grade C)

- What to do before PEI:

  If the nodule is considered suitable for PEI, malignant involvement should be ruled out by US-FNA. Multiple cytologic examinations of the cystic wall should be performed (grade C).

  A thorough US examination should evaluate the position, shape, size, margins, and vascular pattern of the nodule (grade C).

- What to do during PEI (grade D):

  Continuously monitor the position of the needle tip in the nodule and of ethanol diffusion within the nodule.

  Stop the procedure immediately if the patient reports severe pain, begins to cough, or has a change in voice.

Radioiodine

- Consider radioiodine treatment for small goiters (volume <100 mL), in those without suspected malignant potential, in patients with a history of previous thyroidectomy, and in those at risk for surgical intervention (grade B).
- Radioiodine treatment is not the first-line therapy if compressive symptoms are present, if patients have large nodules that require high amounts of radioiodine and may be resistant to treatment, or if immediate resolution of thyrotoxicosis is desired (grade C).
- Radioiodine treatment is effective and safe. Large epidemiologic studies have shown no associated clinically significant increase in the risk of thyroid cancers or leukemia (grade B).
- Give radioiodine therapy cautiously in elderly patients, especially those with heart disease (grade C).
- Radioiodine is contraindicated in pregnant or lactating women. Always perform a pregnancy test before administration of radioiodine in women of childbearing age (grade A).
- Avoid use of iodine contrast agents or iodinated drugs before administration of radioiodine; withdraw antithyroid drugs at least 3 weeks before treatment and resume such regimens 3 to 5 days after radioiodine therapy (grade C).
- Follow-up of patients should include monitoring of serum levels of TSH, free T_4, and free triiodothyronine; consider repeating treatment in 3 to 6 months if TSH is still <0.1 micro-IU/mL (grade C).

Nodules With Indeterminate FNA

- Indeterminate FNA results are due to poorly defined morphologic criteria for distinguishing benign from malignant lesions. No clear-cut cytologic criteria are available to aid in decision making. At surgical intervention, about 20% of indeterminate FNA specimens are malignant lesions.
- Repeated biopsy of these nodules is not recommended because it creates confusion and does not provide additional useful information for management.

- Because large-needle thyroid biopsy is not more accurate than FNA, is more cumbersome, and is associated with pain and occasional severe bleeding, it is currently not recommended in the management of thyroid nodules.
- Clinical criteria such as nodule size (>4 cm), fixation, and age of the patient may suggest increasing risk for malignant potential.
- Currently, we recommend surgical excision of all indeterminate thyroid nodules.

Nodules With Nondiagnostic FNA

- An unsatisfactory (nondiagnostic) FNA specimen usually results from a cystic nodule that yields few or no follicular cells.
- US-FNA directed at the peripheral portion of the lesion is indicated if initial palpation-guided FNA was nondiagnostic.
- Reaspiration yields satisfactory results in 50% of cases.
- Despite good initial technique, rebiopsy, and US-FNA, approximately 5% of thyroid nodules remain nondiagnostic. Such nodules should be surgically excised (grade D).
- Whether routine rebiopsy is necessary is unclear. For physicians or clinics beginning to perform FNA, reaspiration provides reassurance with the procedure. We recommend reaspiration if a nodule enlarges, a cyst reappears, a nodule is larger than 4 to 5 cm, or no shrinkage of the nodule occurs after LT_4 therapy (see Table 19 in the original guideline document).

Thyroid Nodule During Pregnancy

- No evidence indicates that administration of LT_4 is effective in reducing the size or arresting the growth of thyroid nodules during pregnancy; thus, LT_4 therapy during pregnancy is not advisable (grade C).
- For a growing thyroid nodule during pregnancy, follow-up studies should include FNA and US (grade C).
- With a cytologic diagnosis of thyroid cancer during the first or second trimester in a pregnant woman, surgical intervention should be undertaken during the second trimester, when anesthesia risks are minimal. If this cytologic diagnosis is made during the third trimester, postpone surgical treatment until the immediate postpartum period (grade C).
- Pregnancy may cause a misleading diagnosis of follicular neoplasm. The malignancy rate of follicular neoplasm during pregnancy is about 14%. Therefore, defer surgical treatment to the postpartum period (grade C).

Radioiodine Treatment of Nodular Goiter

- In patients with low-uptake MNG given small doses of rhTSH, radioiodine uptake increases >4-fold within 72 hours. Sufficient radiation therapy is delivered to the thyroid to decrease the size and to ameliorate compressive symptoms rapidly.
- Average decrease in goiter size is 40% during the first year and 60% by the end of the second year. In patients with suppressed TSH levels, the TSH value returns to normal or increases within 3 to 6 months.
- Free T_4 and total triiodothyronine levels increase approximately 50% over baseline within 72 hours after injection of rhTSH. Beta-adrenergic or calcium

channel blockers are given to avoid thyroid hormone-mediated adverse effects.
- ^{131}I (30 mCi) is given orally 72 hours after rhTSH. No significant radioiodine-induced sequelae occur immediately. Rarely, immunogenic hyperthyroidism occurs several months after treatment.
- Before treatment, US-FNA should be performed to rule out a malignant lesion.
- Currently, use of rhTSH to augment radioiodine treatment is considered "off-label." In elderly patients or patients with comorbid disorders that preclude anesthesia or surgical intervention, however, rhTSH-augmented radioiodine treatment is effective in management of MNG.

Laser Thermal Ablation

- LTA is a low-cost, rapid, and effective mini-invasive technique for the treatment of benign thyroid nodules causing pressure symptoms or cosmetic complaints.
- The procedure should be performed only in carefully selected cases (high-surgical-risk patients). In most patients, 1 to 3 sessions of LTA or a single treatment with multiple fibers induces a nearly 50% decrease in nodule volume and the amelioration of local symptoms (grade C).
- LTA should be restricted to specialized centers, in light of the need for skilled operators to avoid the risk of major complications (grade D).

Histochemical Markers

- Several laboratories are developing molecular assays to clarify suspicious (indeterminate) FNA results: human bone marrow endothelial cell (HBME)-1, galectin-3, thyroid peroxidase antibodies.
- Most markers show either high sensitivity or high specificity, but not both, for diagnosing thyroid cancer.
- No specific tumor marker is available that will regularly and reliably distinguish benign from malignant thyroid cellular tumors.

Ultrasonographic Media

- First- and second-generation contrast agents provide only ancillary data for diagnosis of malignant thyroid nodules. The variation of time-intensity curves during the transit times of the injected microbubbles offers a modest improvement over the information obtainable with traditional color Doppler or power Doppler examinations (grade D).
- New specifically designed microbubbles and new models of US equipment with specific software are needed to improve the predictive value of contrast-enhanced US for small-parts applications (grade D).

Definitions:

Level of Evidence

1. Well-controlled, generalizable, randomized trial
   Adequately powered
   Well-controlled multicenter trial

Large meta-analysis with quality ratings
All-or-none evidence

2. Randomized controlled trial--limited body of data
   Well-conducted prospective cohort study
   Well-conducted meta-analysis of cohort studies
3. Methodologically flawed randomized clinical trials
   Observational studies
   Case series or case reports
   Conflicting evidence with weight of evidence supporting the recommendation
4. Expert consensus
   Expert opinion based on experience
   "Theory-driven conclusions"
   "Unproven claims"

Recommendation Grade

A. Homogeneous evidence from multiple well-designed randomized controlled trials with sufficient statistical power
   Homogeneous evidence from multiple well-designed cohort controlled trials with sufficient statistical power
   ≥1 conclusive level 1 publications demonstrating benefit >> risk
B. Evidence from at least one large well-designed clinical trial, cohort or case-controlled analytic study, or meta-analysis
   No conclusive level 1 publication; ≥1 conclusive level 2 publications demonstrating benefit >> risk
C. Evidence based on clinical experience, descriptive studies, or expert consensus opinion
   No conclusive level 1 or 2 publication; ≥1 conclusive level 3 publications demonstrating benefit >> risk
   No conclusive risk at all and no conclusive benefit demonstrated by evidence
D. Not rated
   No conclusive level 1, 2, or 3 publication demonstrating benefit >> risk
   Conclusive level 1, 2, or 3 publication demonstrating risk >> benefit

CLINICAL ALGORITHM(S)

Clinical algorithms are provided in the original guideline document for the diagnosis and management of palpable thyroid nodules and for the diagnosis and management of ultrasonography-determined thyroid incidentalomas.

EVIDENCE SUPPORTING THE RECOMMENDATIONS

TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

The evidence supporting the recommendations is identified for selected recommendations (see "Major Recommendations").

Most of the recommendations are based on literature reviews. In areas of uncertainty, professional judgment was applied.

BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

POTENTIAL BENEFITS

Accurate diagnosis and appropriate management of thyroid nodules

POTENTIAL HARMS

- Fine-needle aspiration biopsy of a thyroid nodule often causes slight temporary pain and is occasionally associated with a minor hematoma.
- Levothyroxine (LT_4) treatment should not be targeted toward complete thyroid-stimulating hormone (TSH) suppression. Indeed, sustained subclinical hyperthyroidism is associated with a significant decrease in bone density in postmenopausal women, although no available evidence has indicated an increase in the rate of bone fractures. Moreover, in elderly patients with suppressed levels of serum TSH, a 3-fold increase in atrial fibrillation and increased mortality attributable to cardiovascular diseases have been reported.
- As is the case with all operations, bleeding and infection can occur with surgical treatments. Permanent hypoparathyroidism or injury to the recurrent laryngeal nerve should occur in less than 1% of the cases when the surgical procedure is performed by experienced surgeons.
- Although investigators have indicated that high doses of radioiodine may induce thyroid cancer, other solid tumors, or leukemia, large epidemiologic studies have not shown a clinically significant effect.
- Laser thermal ablation (LTA) induces a burning cervical pain, which rapidly decreases when the energy is turned off. In the few patients treated by this technique to date, no permanent dysphonia, cutaneous burning, or damage to the vital structures of the neck have been reported.
- Adverse effects of percutaneous ethanol injection (PEI) are generally mild and transient. Their occurrence depends on the experience of the center. Mild local pain is common but is rapidly self-resolving or can be controlled with low doses of nonsteroidal anti-inflammatory drugs for 1 to 2 days.
- Transient dysphonia is rare after PEI treatment of cystic lesions. Special care must be taken to avoid seepage of ethanol outside the nodule. Real-time US monitoring during PEI allows verification of the correct position of the needle tip within the nodule and assessment of the distribution of the injected ethanol, which should be recognizable as an expanding hyperechoic area within the cystic cavity. Ethanol seeping outside the cystic nodule is always attributable to incorrect procedure (usually the displacement of the needle tip) and induces chemical damage to the recurrent laryngeal nerve. After confirmation with laryngoscopy of unilateral vocal cord paresis, corticosteroid therapy (betamethasone, 1.5 mg daily) can be administered for a few days. The patients should be reassured that, in most cases, a complete recovery from vocal cord paresis usually occurs within a few weeks.
- In a few patients with severe thyrotoxicosis (rare in cystic autonomously functioning thyroid nodules [AFTN]), the procedure may be followed by transient exacerbation of thyrotoxic symptoms. In most cases, only a slight, transient, and asymptomatic increase in serum thyroid hormone levels is observed.

- Subcutaneous and intracapsular hematomas are rare and self-resolving complications of PEI, provided the patient is not taking anticoagulants (which should be withdrawn at least 48 hours before PEI).

CONTRAINDICATIONS

CONTRAINDICATIONS

- Use of levothyroxine (LT_4) therapy should be avoided in most cases and especially in the following:
    - Large thyroid nodules and goiters, particularly in the presence of symptoms or signs of functional autonomy
    - Clinically suspicious lesions or lesions with an inadequate cytologic sample
    - Postmenopausal women and men older than 60 years
    - Patients with osteoporosis or systemic illness
    - Patients with cardiovascular disease
- Percutaneous ethanol injection (PEI) should not be performed:
    - On solid, cold nodules, unless surgical treatment is contraindicated
    - On large or toxic autonomously functioning thyroid nodules (AFTN) (nodule volume >5 mL)--the rate of cure is too low and relapse is frequent
    - On toxic multinodular goiters (MNGs)
- The only absolute contraindications to radioiodine treatment are pregnancy and lactation.

QUALIFYING STATEMENTS

QUALIFYING STATEMENTS

- American Association of Clinical Endocrinologists Medical Guidelines for Clinical Practice are systematically developed statements to assist health-care professionals in medical decision making for specific clinical conditions. Most of the content herein is based on literature reviews. In areas of uncertainty, professional judgment was applied.
- These guidelines are a working document that reflects the state of the field at the time of publication. Because rapid changes in this area are expected, periodic revisions are inevitable. We encourage medical professionals to use this information in conjunction with their best clinical judgment. The presented recommendations may not be appropriate in all situations. Any decision by practitioners to apply these guidelines must be made in light of local resources and individual patient circumstances.

IMPLEMENTATION OF THE GUIDELINE

DESCRIPTION OF IMPLEMENTATION STRATEGY

An implementation strategy was not provided.

IMPLEMENTATION TOOLS

Clinical Algorithm
Patient Resources

For information about availability, see the "Availability of Companion Documents" and "Patient Resources" fields below.

INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES

IOM CARE NEED

Getting Better

IOM DOMAIN

Effectiveness
Patient-centeredness

IDENTIFYING INFORMATION AND AVAILABILITY

BIBLIOGRAPHIC SOURCE(S)

AACE/AME Task Force on Thyroid Nodules. American Association of Clinical Endocrinologists and Associazione Medici Endocrinologi medical guidelines for clinical practice for the diagnosis and management of thyroid nodules. Endocr Pract 2006 Jan-Feb;12(1):63-102. [142 references]

ADAPTATION

Not applicable: The guideline was not adapted from another source.

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GUIDELINE DEVELOPER(S)

American Association of Clinical Endocrinologists - Medical Specialty Society
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FINANCIAL DISCLOSURES/CONFLICTS OF INTEREST

Not stated

GUIDELINE STATUS

This is the current release of the guideline.

This guideline updates a previous version: AACE clinical practice guidelines for the diagnosis and management of thyroid nodules. Jacksonville (FL): AACE; 1996. 16 p. (AACE clinical guidelines; no. 1996).

GUIDELINE AVAILABILITY

Electronic copies: Available in Portable Document Format (PDF) from the American Association of Clinical Endocrinologists (AACE) Web site.

Print copies: Available from the American Association of Clinical Endocrinologists (AACE), 1000 Riverside Avenue, Suite 205, Jacksonville, FL 32204.

AVAILABILITY OF COMPANION DOCUMENTS

The following is available:

- American Association of Clinical Endocrinologists protocol for standardized production of clinical practice guidelines. Endocrine Pract 2004 Jul/Aug; 10(4):353-61.

Electronic copies: Available in Portable Document Format (PDF) from the American Association of Clinical Endocrinologists (AACE) Web site.

Print copies: Available from the American Association of Clinical Endocrinologists (AACE), 1000 Riverside Avenue, Suite 205, Jacksonville, FL 32204.

PATIENT RESOURCES

The following is available:

- The thyroid nodule. Information for patients. Jacksonville (FL): American Association of Clinical Endocrinologists; 2005. 2 p.

Electronic copies: Available in Portable Document Format (PDF) from the American Association of Clinical Endocrinologists Web site.

Please note: This patient information is intended to provide health professionals with information to share with their patients to help them better understand their health and their diagnosed disorders. By providing access to this patient information, it is not the intention of NGC to provide specific medical advice for particular patients. Rather we urge patients and their representatives to review this material and then to consult with a licensed health professional for evaluation of treatment options suitable for them as well as for diagnosis and answers to their personal medical questions. This patient information has been derived and prepared from a guideline for health care professionals included on NGC by the authors or publishers of that original guideline. The patient information is not reviewed by NGC to establish whether or not it accurately reflects the original guideline's content.

NGC STATUS

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